Contrast-enhanced ultrasound of intrahepatic cholangiocarcinoma: correlation with pathological findings

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Purpose

Intrahepatic cholangiocarcinoma (ICC) is a malignant epithelial tumour that originates at the second branch (segmental branch) or the proximal branch of the intrahepatic bile ducts and is the second most common primary malignant tumour in the liver [1-3]. ICC does not cause clinical symptoms in its early stages and thus it can grow large; indeed, the disease is often advanced when it is first detected [4]. Early diagnosis will increase the resectability and thus improve the prognosis of patients with ICCs. Currently, there are no blood tests or tumour markers specific for ICC and the diagnosis mainly depends on imaging procedures [5].

Baseline ultrasound remains the first-line modality for the detection of ICC, but it has difficulty in differentiating this entity from other focal liver lesions because the sonographic findings are non-specific [6, 7]. Patients suspicious for ICC are usually referred for contrast-enhanced CT (CECT) or MRI examination for characterization [8]. The recently introduced low acoustic power contrast-enhanced ultrasound (CEUS) allows depiction of blood haemodynamics and perfusion within focal lesions [9], and a previous study has found that ICC has some specific findings at CEUS [10]. In this study, the enhancement patterns of ICCs on CEUS and CECT were compared in order to evaluate the difference between the two modalities in depicting the blood haemodynamics and perfusion within ICCs. In addition, the efficacy of both modalities for diagnosing ICC was investigated.

Methods and Materials

From March 2004 to August 2012, 40 patients with histopathologically proven ICCs who had undergone CEUS and CECT examinations in our institution were included in this study retrospectively. The tissue specimens were obtained from surgery or ultrasound guided percutaneous biopsy.

The patients group consisted of 27 men and 13 women. 36 patients had a single nodule, whereas 4 patients had multiple nodules.

In patients with multiple nodules, only the largest nodule visualized on baseline ultrasound was selected for CEUS evaluation. Therefore, a total of 40 nodules were observed and the size of the lesions was measured.

Ultrasound examination
Ultrasound examinations were performed with either an Acuson Sequoia 512 (Siemens Medical Solutions, Mountain View, CA) or GE expert 5 scanner depending on the availability of the machines.

The contrast agent used was SonoVue (Bracco SpA, Milan, Italy), which was administrated intravenously at a dose of 2.4 ml per injection in a bolus fashion (within 1-2 s), followed by a flush of 5 ml of normal saline.

Baseline ultrasound was firstly performed to scan the whole liver; the target lesion was determined, which was subsequently resected or biopsied. The images that clearly exhibited lesion characteristics on baseline ultrasound, including size, echogenicity, shape, boundary, focal bile duct dilation around the tumour and calculus, were recorded.

In the contrast-enhanced study, the mechanical index value ranged from 0.15-0.21 for CPS and no larger than 0.1 for CHI.

Upon initiation of the SonoVue injection, the timer was activated simultaneously. The target lesion was observed continuously for 6 min, without alteration of the imaging setting of the scanner. The entire process, including arterial (8-30 s from the beginning of contrast agent administration), portal (31-120 s), and late (121-360 s) phases, was stored in the hard disk incorporated into the scanner. All of the baseline ultrasound and CEUS examinations were performed by two experienced investigators with more than 5 years' experience in liver CEUS.

Contrast-enhanced CT

CECT examination was performed using a Toshiba Xpress/SX single-slice helical CT scanner (Tokyo, Japan) or Toshiba Aquilion 64-slice helical CT scanner (Tokyo, Japan) within 14 days before or after CEUS examination.

No treatment was performed on the ICCs during the period between CEUS and CECT examinations. Singleslice helical CT parameters included 5 mm collimation, a pitch of 1.0, 120 kV and 250 mAs. The 64-slice helical CT study protocol involved a 0.5 6 64 mm collimation, 120 kV and 150-200 mAs. The standard dual-phase scan procedure was used. After an unenhanced helical sequence scan through the liver, 50-100 ml (1.5 ml kg⁻¹) of non-ionic iodinated contrast material (Ultravist; Schering, Berlin, Germany) was administered via the antecubital vein by power injection at a rate of 3 ml s⁻¹ (single-slice helical CT) or 4 ml s⁻¹ (64-slice helical CT). The arterial phase sequence was obtained 25-32 s after injection, followed by a portal venous phase sequence at 50-60 s.

Image analysis

The images from CEUS were analysed in consensus by two investigators, and the CECT images by two radiologists, who were not involved in the sonographic or CT scanning and
were unaware of the clinical histories, histopathological results and other imaging findings of the patients. The echogenicity of the lesion on baseline ultrasound and attenuation on unenhanced CT with respect to the surrounding normal liver tissue, as well as focal bile duct dilation around the tumour and calculus, were evaluated. On both CEUS and CECT, the enhancement level and pattern, as well as the changes associated with the dynamic phases, were analysed.

On CEUS, the highest enhancement of the lesion was considered if different enhancement levels were present during the arterial phase. The tumour enhancement levels in the arterial phase on CEUS were divided into non-enhancement, hypoenhancement, isoenhancement and hyperenhancement, compared with the adjacent liver parenchyma, in accordance with "Guidelines for the use of contrast agents in ultrasound.

The enhancement pattern was determined by evaluating images obtained during the early phase of enhancement (typically 10-30 s after contrast agent administration), when the enhancement of the tumour had just commenced. The enhancement pattern on CECT was determined by evaluating the arterial phase images.

The enhancement pattern of the lesion was classified as follows [10]:

Non-enhancement - no appearance of contrast material in the lesion.

Peripheral irregular rim-like hyperenhancement - irregular rim-like hyperenhancement at the peripheral portion of the lesion and inhomogeneous hypoenhancement at the central portion, with strip-like enhancement extending to the central portion of the lesion.

Diffuse heterogeneous hyperenhancement - heterogeneous hyperenhancement at both the periphery and the central portion of the lesion.

Diffuse homogeneous hyperenhancement - homogeneous hyperenhancement at both the periphery and the central portion of the lesion.

Diffuse heterogeneous hypoenhancement - heterogeneous hypoenhancement at both the periphery and the central portion of the lesion.

The intratumoral blood vessels that appeared during arterial phases were also evaluated on both CEUS and CECT. The enhancement level of the lesion at the end of the portal phase on CEUS was determined. In this late phase, the enhancement level was recorded either when the lesion showed hypoenhancement or 360 s after contrast agent administration. A comparison of the enhancement appearance in the late phase between CEUS and CECT was not performed as the routine scanning protocol of CECT did not include late-phase scanning in our institution.

To evaluate the accuracy of CEUS and CECT in diagnosing ICC prior to pathological examination, the diagnostic results of CEUS and CECT (which were made by
experienced radiologists) were also recorded. The sonographic diagnostic criteria for ICC were as follows: a non-cirrhotic liver; variable echogenicity; an irregular lesion margin; peripheral bile duct dilatation or calculus on baseline ultrasound; peripheral irregular rim-like hyperenhancement, heterogeneous hypoenhancement or heterogeneous hyperenhancement during the arterial phase; and hypoenhancement during the portal and late phases on CEUS [10, 12-14]. The diagnostic criteria of CECT were based on previous studies [6, 15-17].

**Statistical analysis**

The quantitative data were expressed as mean ± standard deviation. The McNemar test was used to evaluate differences between paired qualitative data. The enhancement pattern of the lesion in terms of lesion size was identified by means of the $\chi^2$ test. Two-tailed $p \leq 0.05$ was considered statistically significant.

Statistical analyses were performed using the SPSS 11.0 software package (SPSS Inc., Chicago, IL).

**Results**

On baseline ultrasound, the mean diameter of all lesions was 6.7-3.1 cm (range, 2.1-15.5 cm). The depth from the body surface to the bottom of the lesion ranged from 3.7 cm to 16.0 cm. The numbers of lesions that showed hypoecho-genicity, hyperecho-genicity and mixed echogenicity were 16 (40.0%), 5 (12.5%) and 19 (47.5%), respectively. On unenhanced CT, 39 (97.5%) lesions were hypoattenuating relative to the liver parenchyma; the remaining 1 lesion (2.5%) was hyperattenuating.

Intrahepatic bile duct dilation around the tumour was presented in 22 (55.0%) lesions, and calculus in the bile duct was seen in 11 (27.5%) lesions on both CEUS and CECT.

During the arterial phases of CEUS and CECT, four types of enhancement pattern were observed: peripheral irregular rim-like hyperenhancement (Type I) (Figure 1); diffuse heterogeneous hyperenhancement (Type II) (Figure 2); diffuse homogeneous hyperenhancement (Type III); and diffuse heterogeneous hypoenhancement (Type IV) (Figure 3). The numbers of the lesions that showed the above-mentioned patterns (Types I-IV) were 19 (47.5%), 9 (22.5%), 5 (12.5%) and 7 (17.5%), respectively. On CECT, the numbers were 22 (55.0%), 3 (7.5%), 2 (5.0%) and 13 (32.5%), respectively.

The McNemar test indicated no significant difference between CEUS and CECT with respect to either the enhancement level ($p = 0.109$) or the enhancement pattern ($p = 0.125$) (Table 1). There were significant differences among the four types of enhancement pattern by lesion size on CEUS ($p = 0.017$) (Table 2).
In the portal phase, 39 (97.5%) lesions were hypoenhancing on CEUS, whereas 25 (62.5%) were hypoenhancing on CECT.

Intratumoral vessels were exhibited in 20 lesions (50.0%) on CEUS and 9 lesions (22.5%) on CECT (McNemar test, p<0.019). A wedge or patch-like hyperenhanced area in adjacent normal liver was visualized for 5 lesions (12.5%) during the arterial phase on CEUS and for 8 lesions (20.0%) on CECT (McNemar test, p<0.25).

CEUS correctly diagnosed 32 (80.0%) lesions prior to pathological examination. Among the incorrectly diagnosed lesions, six showing diffuse homogeneous hyperenhancement in the arterial phase and hypoenhancement in the portal phase were misdiagnosed as hepatocellular carcinoma (HCC); two lesions showing peripheral rimlike hyperenhancement in the arterial phase and hypoenhancement in the portal phase were misdiagnosed as metastatic liver cancer (MLC). CECT made a correct diagnosis in 27 (67.5%) lesions. There were four lesions misdiagnosed as HCC, three lesions misdiagnosed as MLC and six lesions misdiagnosed as inflammatory masses. The McNemar test indicated no significant difference in the diagnostic accuracy between CEUS and CECT (p<0.18).

**Images for this section:**

(a)  
(b)  
(c)  
(d)  
(e)  
(f)
**Fig. 1:** Intrahepatic cholangiocarcinoma. (a) Baseline ultrasound shows an ill-defined isoechoic mass (arrows). (b) CEUS shows peripheral rim-like hyperenhancement (arrowheads) around the tumor during the arterial phase, but hypoenhancement in the central portion. (c-d) In the portal and late phase, the whole lesion shows hypoenhancement. (e) Microscopically, pathological examination reveals abundant tumor cells in the peripheral portion of the tumor. (f) There are scarce tumor cells in the central portion of the tumor and fibrosis is prominent.

![Fig. 1](image1)

**Fig. 2:** Figure 2. Periphery cholangiocarcinoma in a 67-year-old woman. (a) Baseline ultrasound shows a mixed echoic nodule (arrows), 9.9 cm in size, in segments 2 and 3. (b) On contrast-enhanced ultrasound (CEUS), the nodule (arrows) appears as diffuse heterogeneous hyperenhancement compared with the adjacent liver parenchyma during the arterial phase (12 s after contrast agent administration). (c) In the portal phase (73 s after contrast agent administration), the nodule (arrows) appears as heterogeneous hypoenhancement on CEUS. (d-f) The nodule (arrows) presents as hypoattenuation on (d) unenhanced CT, diffuse heterogeneous hypoenhancement (arrows) in (e) the arterial phase and heterogeneous hypoenhancement (arrows) in the portal phase on (f) contrast-enhanced CT. (e) A wedge or patch-like hyperenhanced area in the adjacent normal liver (arrowhead) was visualized.

![Fig. 2](image2)
Fig. 3: Intrahepatic cholangiocarcinoma. (a) Baseline ultrasound shows an iso-echoic mass (calipers) in the right lobe of the liver. (b) The lesion (arrows) shows homogeneous hyperenhancement during the arterial phase. (c) The lesion (arrows) becomes slightly hypo-enhancing during the portal phase. (d) The lesion (arrows) becomes hypo-enhancing during the late phase. (e, f) Microscopically, abundant tumour cells are present in both the peripheral portion (e) and the centre portion (f) (haematoxylin-eosin stain, 6200 magnification).
Fig. 4: Figure 4. Intrahepatic cholangiocarcinoma. (a) Baseline ultrasound shows an ill-defined iso-echoic mass (arrows) in the left lobe of the liver. (b) The lesion (arrows) shows heterogeneous hypo-enhancement during the arterial phase. (c) The lesion (arrows) remains hypo-enhancing during the portal phase. (d) The lesion (arrows) continues to be hypo-enhancing during the late phase. (e, f) Microscopically, scarce tumour cells are present in both the peripheral portion (e) and the centre portion (f) (haematoxylin-eosin stain, 6200 magnification).

<table>
<thead>
<tr>
<th>Enhancement patterns</th>
<th>Distribution of tumour cells in the peripheral portion</th>
<th>Distribution of tumour cells in the central portion</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Score 1  Score 2  Score 3</td>
<td>Score 1  Score 2  Score 3</td>
</tr>
<tr>
<td>Peripheral irregular rim-like hyperenhancement (n=19)</td>
<td>0 (0)      8 (42.1)  11 (57.9)</td>
<td>18 (94.7) 1 (5.3)  0 (0)</td>
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<td>Heterogeneous hyperenhancement (n=6)</td>
<td>0 (0)      4 (66.7)  2 (33.3)</td>
<td>1 (16.7)  5 (83.3)  0 (0)</td>
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<tr>
<td>Homogeneous hyperenhancement (n=3)</td>
<td>0 (0)      1 (33.3)  2 (66.7)</td>
<td>1 (33.3)  0 (0)  2 (66.7)</td>
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<td>Heterogeneous hypo-enhancement (n=4)</td>
<td>2 (50.0)  2 (50.0)  0 (0)</td>
<td>3 (75.0)  1 (25.0)  0 (0)</td>
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<tr>
<td>Total (n=32)</td>
<td>2 (6.3)  15 (46.9)  15 (46.9)</td>
<td>23 (71.9) 7 (21.9)  2 (6.3)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.007*                              &lt;0.001*</td>
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Fig. 5
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<th>Enhancement patterns</th>
<th>Distribution of fibrosis in the peripheral portion*</th>
<th>Distribution of fibrosis in the central portion*</th>
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<td></td>
<td>Score 1</td>
<td>Score 2</td>
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<td>p-value</td>
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<td>0.693</td>
</tr>
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</table>

Fig. 6
Conclusion

The most common imaging finding of ICC on baseline ultrasound is of a solid mass with irregular borders [4,13], although this is non-specific. Ancillary findings, including perilesional bile duct dilation, calculus in the lesion or bile duct and capsular retraction [18], are helpful to aid diagnosis, but it is still difficult for baseline ultrasound to distinguish ICC from other liver lesions such as HCC, liver metastasis and inflammatory liver lesions [13].

CECT has the advantages of improved resolution and better anatomic detail, and facilitates the investigation of intralesional haemodynamics. The accuracy of CECT in diagnosing ICC was 70% [19]. On unenhanced CT, ICC is depicted as a well-defined mass of markedly low attenuation with irregular borders. On enhanced CT, the typical appearance is of a mass that demonstrates thin, mild, rim-like enhancement at the periphery and markedly low intratumoral attenuation with amorphous areas of slightly high attenuation during both the arterial and portal venous phases [6, 15, 16].

Like CECT, the recently introduced real-time CEUS allows depiction of the intralesional haemodynamics and blood perfusion in ICCs [9, 10, 20]. Previous studies have shown that ICCs have some special features on CEUS during the arterial phase. ICCs show three main enhancement patterns: (i) peripheral rim-like hyperenhancement, (ii) inhomogeneous hypoenhancement of the whole tumour and (iii) inhomogeneous hyperenhancement [14, 21, 22], with visualization rates of 44.4%, 44.4% and 11.2%, respectively [10]. These results suggest that CEUS might be used as a characterization tool for ICC.

Nevertheless, no studies have yet been carried out to compare the enhancement patterns of ICC on CEUS and CECT.

In the current study, the typical enhancement pattern - irregular rim-like hyperenhancement at the periphery of the lesion with strip-like enhancement extending to the central portion - was demonstrated in the majority (47.5%) of ICCs on CEUS, which was consistent with findings on CECT (visualization rate of 52.5%). Three other types of enhancement pattern were visualized on both CEUS and CECT, including diffuse heterogeneous hyperenhancement, diffuse heterogeneous hypoenhancement and diffuse homogeneous hyperenhancement. No significant difference in the visualization of the four enhancement patterns was found between CEUS and CECT. The different enhancement patterns may relate to different pathological components in the tumour [23]. When there is abundant fibrous stroma in the tumour, it might show hypoenhancement in the arterial phase. If the ICC is rich in tumour cells at the peripheral portion and fibrosis occurs in the central portion, it might appear as irregular peripheral rim-like hyperenhancement. Conversely, the tumour might show diffuse hyperenhancement if the major component is tumour cells and there is no central necrosis [2,4,17,24,25].
Our study indicated that the enhancement pattern may also correspond to tumour size, i.e. smaller lesions tend to show homogeneous hyperenhancement that is hard to differentiate from HCC, whereas larger lesions tend to show diverse enhancement patterns. Zhang et al [26] postulated that this phenomenon may reflect pathological change along with tumour growth, i.e. larger tumours may compress central vessels as they grow, resulting in central hypovascularity or necrosis.

In this series, six ICCs showed hyperenhancement immediately after contrast agent injection; washout was very fast, leading to hypoenhancement 24-27 s after contrast agent administration on CEUS. However, the six ICCs were depicted as hypoenhancement during the arterial phase on CECT. This difference may be attributed to the real-time scanning characteristic of CEUS. The CEUS feature of continuous and dynamic observation facilitates documentation of the entire enhancement process, whereas CECT might miss the information during the time window and thus only hypoenhancement was visualized.

On CT, most (97%) ICCs showed no apparent change between the hepatic arterial and the portal venous phases, remaining isoattenuating or slightly hyperattenuating [15, 27-29]. However, most (97.5%) ICCs in this series showed enhancement fadeout and appeared as hypoenhancement during the portal venous and delayed phases on CEUS, which is a typical feature of liver malignancy [12, 30]. The phenomenon might be explained by the fact that the ultrasound contrast agent is a real blood pool agent and thus it does not diffuse through the vascular endothelium into the interstitium. Conversely, the CT contrast agent can diffuse into the interstitial spaces of the tumour slowly from the intratumoral vessels, and clear up slowly owing to the abundant fibrous tissue and slow blood flow in ICCs; therefore, even delayed tumour enhancement was visualized [27, 31].

A significant difference in the ability to exhibit intratumoral vessels was found between CEUS and CECT, with the visualization rates being 50% and 23%, respectively. This may reflect the real-time scanning, as well as the high spatial and temporal resolution, of CEUS, which can record the display of intratumoral vessels completely. Conversely, the pathological change of a wedge or patch-like hyperenhanced area in adjacent liver during the arterial phase was visualized on both CEUS and CECT, and no difference between these modalities was detected. The phenomenon is a reflection of hepatic arterial flow increasing to compensate for the decrease in portal venous flow, which is caused by the narrowing or obstruction of the portal vein from invasion or extrinsic compression by the tumour [6]. However, this finding is non-specific and can be found in other focal liver lesions.
Initial results found that the diagnostic accuracy of CEUS and CECT for ICCs before pathological examination was almost the same, which suggested that CEUS might also be used as a characterization tool for ICCs.

The enhancement patterns of ICC are variable; some might be characteristic, such as peripheral irregular rimlike enhancement, whereas others should be taken into consideration in order to differentiate from other more common intrahepatic masses, such as MLC and HCC.

Hypovascular metastases, especially from adenocarcinoma of the gastrointestinal tract, frequently show a peripheral rim-like enhancement pattern similar to that of ICC [12, 14]. Absence of the possible primary site, other ancillary findings (e.g. bile duct dilation) and the irregular shape of the lesion can be clues useful for differentiation [6]. It is difficult to distinguish HCC from some ICCs showing diffuse hyperenhancement in the arterial phase and subsequent washout. A background of virus hepatitis B or C, the presence of liver cirrhosis, elevation of a-fetoprotein, and the absence of peripheral bile duct dilation and calcification in the tumour may all be useful for ruling out ICC [13, 23].

The major limitation of this study was that a comparison of the enhancement appearance in the late phase between CEUS and CECT was not performed, although the late phase of CEUS was well recorded in the present study. According to the literature [17, 27, 31], delayed intratumour contrast enhancement is a typical feature of ICC on CECT [27], occurring in 74% of patients with ICCs [32], which is recorded as a mild or marked increase in tumour attenuation with progressive and concentric filling of contrast material on delayed phase images [27, 33]. In the present study, all 40 ICC lesions appeared as hypoenhancement with conspicuous contours during the late phase on CEUS. This also might be related to the different characteristics of sonographic contrast agents and CT contrast material, as mentioned above. The other limitation was that the diagnostic efficacies of CEUS and CECT for ICCs were not fully compared. The comparison of diagnostic performance using receiver operating characteristic analysis, including other liver tumours, and a prospective protocol are mandatory in future studies.

Conclusions

The enhancement patterns of ICCs on CEUS were consistent with those on CECT in the arterial phase, whereas in the portal phase ICCs faded out more obviously on CEUS than on CECT. CEUS had the same accuracy as CECT for diagnosing ICCs, and thus could be used as a new modality for the characterization of ICCs.

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Enhancement patterns of ICC: comparison between CEUS and CECT

**Personal Information**